

# Tetracycline in nongonococcal urethritis

## Comparison of 2 g and 1 g daily for seven days

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**SUMMARY** In a previous study treatment with minocycline 100 mg orally every day for seven days was as effective for nongonococcal urethritis (NGU) as 200 mg for seven days or 100 or 200 mg for 21 days. In this prospective, randomised study men with NGU received tetracycline either 500 mg or 250 mg four times daily for seven days. Of 200 men initially enrolled, *Chlamydia trachomatis* was isolated from 40% and *Ureaplasma urealyticum* from 48%. Eight of 10 homosexual men compared with 39 (21%) of 190 bisexual or heterosexual men had negative culture results for both *C trachomatis* and *U urealyticum* ( $\chi^2 = 15.5$ ,  $P < 0.0005$ ). *U urealyticum* was isolated more frequently from chlamydia-negative men and from men with 10 or fewer sex partners during their lifetime. Both regimens were equally effective in their in-vivo activity against *C trachomatis* and *U urealyticum*. Failure rates were similar with the two regimens. More obvious failure with purulent or profuse mucoid discharge and pyuria occurred more frequently with the 250-mg regimen (20% of 76 men on the 250-mg regimen compared with 7% of 67 men on the 500-mg regimen;  $\chi^2 = 4.45$ ,  $P < 0.05$ ). Failure occurred more frequently in men who were initially chlamydia-negative and in men in whom *U urealyticum* persisted after medication. Thus, the 250-mg regimen appeared to be as effective as the 500-mg regimen in the initial treatment of NGU. However, one-third of men had persistent or recurrent urethritis with these regimens, and there is a need for antimicrobial agents with greater in-vivo activity, especially against chlamydia-negative NGU.

### Introduction

One standard treatment for nongonococcal urethritis (NGU) is tetracycline hydrochloride 500 mg four times daily for seven days. A previous study showed that minocycline 100 mg once daily for seven days was as effective as 100 mg twice daily for seven days (or 100 mg once or twice daily for 21 days).<sup>1</sup> Thus, a lower dose of tetracycline than 500 mg four times daily might be equally effective. This would be less expensive and would possibly produce fewer side effects. Consequently, in this study the results with tetracycline 250 mg four times daily for seven days (250-mg regimen) were compared with those with tetracycline hydrochloride 500 mg four times daily for seven days (500-mg regimen) in the treatment of NGU.

Previous studies with tetracyclines have shown that chlamydia-positive NGU responds better to treatment than chlamydia-negative NGU.<sup>1-3</sup> Consequently, cultures were performed for *C trachomatis*, a known cause of 30-50% of cases of NGU, and for *Ureaplasma urealyticum*, a probable cause of some cases of NGU.<sup>4</sup> Response to treatment was correlated with the organism initially isolated to determine if a lower-dose regimen was less effective for a subgroup of cases. Secondary aims were to evaluate further the importance of *U urealyticum* as a cause of NGU and to evaluate the course in men who have pyuria without a purulent or profuse mucoid discharge at follow up.

### Materials and methods

#### STUDY POPULATION

Men were seen at the Provincial Health Building Sexually Transmitted Diseases Clinic in Vancouver. The criteria for admission to the study were: the

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presence of notable pyuria (described below) and obvious urethral discharge, one or more symptoms of urethral discharge, urethral itch, or dysuria for one month or less, no treatment with antimicrobial agents within the preceeding month, and a negative result on Gram stain and subsequently a negative urethral culture result for *Neisseria gonorrhoeae* in men who had not voided in the previous two hours.

#### PRE-TREATMENT EVALUATION

At the initial visit men underwent a standardised interview and genital examination. Urethral exudate was examined by Gram stain and culture on Thayer-Martin medium to exclude gonorrhoea. A calcium alginate urethrogenital swab (Inolex, Glenwood, Illinois) was inserted into the urethra 1-2 cm beyond the fossa navicularis and was then placed in 0.2 mol/l sucrose phosphate transport medium and frozen at  $-70^{\circ}\text{C}$  for subsequent isolation of *C trachomatis*. The first 10-15 ml of urine was then collected and cultured quantitatively for *U urealyticum*. Approximately 7 ml of urine was centrifuged at  $500\times g$  for 10 minutes. The supernatant was discarded and the sediment suspended in 0.5 ml of residual urine. This was poured on to a slide to cover approximately  $1\text{ cm}^2$  and a cover slip overlaid. The slide was examined microscopically ( $\times 400$  magnification) for trichomonads and cells. The presence of 20 or more polymorphonuclear leucocytes (PMNL) in at least two of five fields was considered to represent pyuria.

#### MICROBIOLOGY

Cultures for *C trachomatis* were performed using the method of Wentworth and Alexander.<sup>5</sup> All specimens which gave initially negative results were passed once; that is, if chlamydial inclusions were not detected in the initial culture, duplicate unstained vials were frozen at  $-70^{\circ}\text{C}$ , thawed, and then used to inoculate fresh monolayers of McCoy cells. Cultures for *U urealyticum* were performed in bromothymol blue broth.<sup>6</sup> The urine was diluted  $10^{-1}$ ,  $10^{-3}$ , and  $10^{-5}$  in bromothymol blue broth to quantitate the *U urealyticum*.

#### THERAPY AND FOLLOW UP

Men were randomly assigned to either the 250-mg or the 500-mg (four times daily for seven days) treatment regimens. The men and the clinicians, but not the laboratory staff, knew which dose was being received. The men were asked to return for follow up at 10, 21, and 42 days after the start of therapy. They arrived for these visits when they had not voided for at least four hours. They were questioned about symptomatology, side effects of therapy, and interim sexual activity and were examined for urethral

discharge. A urethrogenital swab was inserted 1-2 cm beyond the fossa navicularis for chlamydial cultures; the first-voided urine was examined for trichomonads and PMNL and cultured quantitatively for *U urealyticum*.

Response to treatment was divided into four categories: (1) pyuria, plus a purulent or profuse mucoid discharge, between  $21\pm 7$  and  $42\pm 7$  days after the start of treatment was called NGU; (2) pyuria with no, or minimal, non-purulent discharge which was present at  $42\pm 7$  days after the start of therapy was called urine failure (both men with NGU and urine failure were called treatment failures); (3) pyuria with no, or minimal, non-purulent discharge at some time seven or more days after the start of treatment but which cleared by  $42\pm 7$  days after the start of treatment was called slow response; and (4) no pyuria and no, or minimal, non-purulent discharge with follow up for  $42\pm 7$  days after the start of treatment was called normal (men who were normal or had a slow response were called responders).

#### STATISTICS

The proportions of groups affected by selected variables were compared by the  $\chi^2$  test with Yates's correction.<sup>7</sup>

#### Results

##### ISOLATION

Two hundred men fulfilled the criteria for the study. There were no significant differences in the initial isolation rates for patients given the two regimens. The initial isolation rates for *C trachomatis* and *U urealyticum* are shown in table I according to sexual preference. Overall, *C trachomatis* was isolated from 40% and *U urealyticum* from 48% of patients. Eight of 10 homosexual men compared with 39 (21%) of 190 bisexual or heterosexual men had negative culture results for both *C trachomatis* and *U urealyticum* ( $\chi^2 = 15.5$ ,  $P < 0.0005$ ).

TABLE I Initial isolation results for urethral cultures for *C trachomatis* and first-voided urine cultures for *U urealyticum* from men with nongonococcal urethritis, according to sexual preference

Sexual preference	No of isolates				Total
	C + U +	C + U -	C - U +	C - U -	
Homosexual			2	8	10
Bisexual	1	1	1	2	5
Heterosexual	21	57	70	37	185
Total (%)	22 (11)	58 (29)	73 (37)	47 (24)	200

C + = *C trachomatis*-positive; C - = *C trachomatis*-negative  
U + = *U urealyticum*-positive; U - = *U urealyticum*-negative

Initial isolation of *C trachomatis* was not correlated with the total number of partners. *U urealyticum* was isolated from 22 (28%) of 80 chlamydia-positive compared with 73 (61%) of 120 chlamydia-negative men ( $\chi^2_1 = 21.4$ ,  $P < 0.0005$ ) and from 39 (66%) of 59 men with 10 or fewer admitted sexual partners in their lifetime compared with 56 (40%) of 141 men with 11 or more partners in their lifetime ( $\chi^2 = 11.6$ ,  $P < 0.001$ ). Cultures for both *C trachomatis* and *U urealyticum* gave negative results in five (8%) of 59 men with 10 or fewer partners in their lifetime compared with 42 (30%) of 141 men with 11 or more ( $\chi^2_1 = 10.5$ ,  $P < 0.005$ ).

#### TREATMENT RESPONSE ACCORDING TO REGIMEN

Response to treatment according to the initial isolation results for *C trachomatis* and *U urealyticum* and also to the treatment regimen are shown in table II. Failure by  $42 \pm 7$  days after the start of treatment occurred in 28 (37%) of 76 men receiving 250 mg compared with 22 (33%) of 67 men receiving 500 mg ( $\chi^2 = 0.25$ , not significant). However, significantly more men on the 250-mg regimen failed with notable pyuria plus a purulent or profuse mucoid discharge (NGU). NGU by  $42 \pm 7$  days after the start of treatment occurred in 15 (20%) of 76 men on the 250-mg regimen compared with five (7%) of 67 men on the 500-mg regimen ( $\chi^2_1 = 4.45$ ,  $P < 0.05$ ).

#### TREATMENT RESPONSE ACCORDING TO INITIAL CULTURE RESULTS

Response to therapy according to initial culture results is shown in table II. Failure occurred in 13 (22%) of 59 chlamydia-positive men compared with 37 (44%) of 84 chlamydia-negative men ( $\chi^2 = 7.4$ ,  $P < 0.01$ ). Pyuria plus a purulent or profuse mucoid discharge (NGU) was present at follow up by  $42 \pm 7$  days after the start of treatment in 0 of 59 chlamydia-

positive men compared with 20 (24%) of 84 chlamydia-negative men ( $\chi^2 = 14.4$ ,  $P < 0.0005$ ).

NGU occurring by  $21 \pm 7$  days after the start of treatment was correlated with the initial isolation and subsequent persistence of *U urealyticum*. Among initially *U urealyticum*-positive men, seven (33%) of 21 men who remained *U urealyticum*-positive after treatment compared with five (9%) of 57 men who became *U urealyticum*-negative had NGU ( $\chi^2 = 5.4$ ,  $P < 0.05$ ). If only men without sexual re-exposure by  $21 \pm 7$  days after the start of treatment are examined, NGU occurred in five of eight who remained *U urealyticum*-positive compared with two of 30 who became *U urealyticum*-negative ( $\chi^2_c = 14.2$ ,  $P < 0.0005$ ).

Neither regimen was significantly more effective in treating NGU caused by *C trachomatis* or *U urealyticum*. Among chlamydia-positive men, failure occurred in five (17%) of 29 men on the 250-mg regimen compared with eight (27%) of 30 on the 500-mg regimen ( $\chi^2 = 0.76$ ,  $P > 0.30$ ). Among chlamydia-negative men, failure occurred in 23 (49%) of 47 men on the 250-mg regimen compared with 14 (38%) of 37 on the 500-mg regimen ( $\chi^2 = 1.03$ ,  $P > 0.30$ ). Among *U urealyticum*-positive men, failure occurred in 17 (40%) of 42 on the 250-mg regimen compared with nine (30%) of 30 on the 500-mg regimen ( $\chi^2 = 0.83$ ,  $P > 0.30$ ). Among *U urealyticum*-negative men, failure occurred in 11 (32%) of 34 on the 250-mg regimen compared with 13 (35%) of 37 on the 500-mg regimen ( $\chi^2 = 0.06$ ,  $P > 0.70$ ).

#### CULTURE RESULTS AT FOLLOW UP

Two men on the 500-mg regimen became chlamydia-positive at follow up (table III). One was initially chlamydia-negative and became culture-positive at the third follow-up visit. The other was initially chlamydia-positive and became culture-positive

TABLE II Response of NGU to treatment according to initial isolation results for *C trachomatis* and *U urealyticum* and treatment regimen (250-mg or 500-mg)\*

Response/category	Initial culture results				Regimen	
	C + U +	C + U -	C - U +	C - U -	250-mg	500-mg
Failures						
(1) NGU			12	8	15	5
(2) Urine failure	1	12	13	4	13	17
Total	1	12	25	12	28	22
Responders						
(3) Slow response	7	4	6	5	10	12
(4) Normal	10	25	23	13	38	33
Total	17	29	29	18	48	45
Total	18	41	54	30	76	67

\*Both doses of tetracycline were given four times daily for seven days.

C + = *C trachomatis*-positive; C - = *C trachomatis*-negative

U + = *U urealyticum*-positive; U - = *U urealyticum*-negative

TABLE III Culture results for *C trachomatis* and *U urealyticum* at follow up according to response to treatment

Response	No of patients			
	C+ U+	C+ U-	C- U+	C- U-
NGU*		1	11	8
Urine failure†	1		5	24
Slow response†			7	15
Normal†			21	50

\*Culture results at the time that NGU was diagnosed

†Culture results at 42 ± 7 days after start of treatment

C+ = *C trachomatis*-positive; C- = *C trachomatis*-negativeU+ = *U urealyticum*-positive; U- = *U urealyticum*-negative

again at the second follow-up visit. Both had had sexual intercourse with new partners before the follow-up culture gave positive results. In all other men, cultures for *C trachomatis* gave negative results at follow up. Of the remaining men, 11 (58%) of 19 men with NGU, five (17%) of 29 urine failures, seven (32%) of 22 with slow response, and 21 (30%) of 71 who were normal were chlamydia-negative, *U urealyticum*-positive at follow up. The rest were chlamydia-negative, *U urealyticum*-negative. Positive culture results for *U urealyticum* were significantly more frequent in men with NGU compared with urine failure ( $\chi^2 = 5.1$ ,  $P < 0.025$ ), and in men with NGU compared with men with normal findings ( $\chi^2 = 4.42$ ,  $P < 0.05$ ). The presence of *U urealyticum* at 21 ± 7 days among initially *U urealyticum*-positive men occurred in 13 (28%) of 46 men on the 250-mg regimen compared with eight (25%) of 32 on the 500-mg regimen ( $\chi^2 = 0.10$ ,  $P > 0.70$ ).

#### PYURIA AT FOLLOW UP

At follow up, an attempt was made to delay retreatment of men with pyuria to determine if the pyuria was a transient event or whether it would persist in the absence of treatment. All six men with pyuria plus a purulent or profuse mucoid discharge had pyuria at the next visit. Three had purulent or profuse mucoid discharge. Among 88 patients showing pyuria with no, or minimal, non-purulent discharge, pyuria was present in 60 (68%) at the next follow up. In the remaining 28 (32%) patients the urine was normal at the next visit. However, six (21%) of these 28 showed pyuria again at the next visit.

#### Discussion

This randomised, but not double-blind, study has shown that the 250-mg regimen of tetracycline is as effective in eradicating *C trachomatis* and *U urealyticum* as the 500-mg regimen, and that by six

weeks after the start of treatment both regimens were associated with persistence or recurrence of NGU in one-third of the men studied.

It was previously shown that minocycline 100 mg once daily for seven days eradicated *C trachomatis* and produced similar clinical results by six weeks after treatment as 100 mg twice daily for seven days, and 100 mg once or twice daily for 21 days.<sup>1</sup> Thus the results in this study are not unexpected. They leave unanswered the question whether or not even lower doses or, better still, less frequent doses of tetracycline will be equally effective. Side effects were not a problem with either dose of tetracycline in the men in this study.

The importance of *U urealyticum* as a urethral pathogen remains uncertain. Although there are some contradictory data, there is mounting evidence that *U urealyticum* is a urethral pathogen. In three recent studies in Seattle<sup>1,8,9</sup> and a study in San Francisco,<sup>10</sup> *U urealyticum* was isolated more often from chlamydia-negative compared with chlamydia-positive men. Persistence of *U urealyticum* after treatment with sulphonamides,<sup>8,9</sup> aminocyclitols, rifampicin,<sup>11</sup> low-dose tetracycline,<sup>12</sup> and minocycline<sup>1</sup> is associated with a higher failure rate. Intraurethral inoculation of primates<sup>13</sup> and humans<sup>14</sup> is associated with urethritis. Thus, the higher rate of isolation of *U urealyticum* from chlamydia-negative men, and the presence of pyuria and a purulent or profuse mucoid discharge in a greater proportion of initially *U urealyticum*-positive men with persistent *U urealyticum* at follow up compared with men in whom *U urealyticum* was eradicated further supports the importance of *U urealyticum* as a urethral pathogen in some men from whom it is initially isolated.

The higher rate of NGU at follow up in men with persistent *U urealyticum* could be artifactual since only first-voided urine samples were cultured. In men with urethritis, intraurethral swabs and first-voided urine samples yield similar rates of isolation of *U urealyticum* (W R Bowie, unpublished data). In some studies of men without urethritis however swabs were reported to yield *U urealyticum* more often than urine specimens.<sup>15</sup> It is not clear if these were specimens of first-voided urine. In our own serial studies of other men, cultures of first-voided urine specimens for *U urealyticum* have been consistent whether or not pyuria was present (W R Bowie, unpublished data).

It is concluded that the 250-mg regimen eradicated *C trachomatis*, that NGU at follow up is correlated with persistent *U urealyticum* in initially *U urealyticum*-positive men, and that the 250-mg regimen is adequate for the initial treatment of men with NGU. However, this regimen should not be

used if gonorrhoea has not been excluded. As in other studies with intensive follow up, there is a disturbingly high (35%) failure rate. New medications must be evaluated in the treatment of NGU, especially chlamydia-negative NGU. Further studies are required to define the cause of chlamydia-negative and *U urealyticum*-negative NGU in heterosexual and homosexual men.

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